Quantitative Microautoradiographic Study of 18F-FDG Distribution in Mouse Intratumoral Cellular Elements

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Introduction

The mechanism of accumulation of 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) into the malignant tissue has been considered to be due to the enhanced rate of glucose utilization by neoplastic cells[1-3]. However, in a recent autoradiographic study, we demonstrated a higher FDG uptake in macrophages than in tumor cells in tumor tissues[4]. Both human and animal tumors are known to be characterized by the macrophage infiltration[5]. It is important to examine the glucose utilization rates in the complex of heterogeneous cell elements in a malignant tumor tissue. In this study, we determine the FDG uptake in each cellular elements in mouse FM3A tumor tissue by a quantitative microautoradiographic analysis.

Materials and Methods

Animals used in this study were maintained in the animal care facility of our institution and the study protocol was approved by the laboratory animal care and use committee of Tohoku University.

C3H/He mice were subcutaneously injected with FM3A tumor cells on their thighs. Ten days following transplantation, eight mice were injected intravenously with 1 mCi (37 MBq) of FDG and killed 1 hr later. The tumors were quickly dissected and prepared for frozen sectioning as described previously[4]. Briefly, under a safety light, the 5 μm-thick sections were directly mounted on slides coated with NTB2 nuclear emulsion (Kodak) and exposed for 4 hr under a dry-ice cold. After the exposure, they were developed, fixed and stained. Silver grain numbers were counted in various tumor regions under a transmitted light bright field microscope using a micrometer. A linear relationship between the number of grains (Y, grains/100 μm^2) and the corresponding FDG radioactivity (X, fCi/100 μm^2) has been observed ($Y=0.4171X+0.3538$, $r=0.9996$)[4].

Results

Table 1 shows the results of grain counting for FDG microautoradiograms of tumor sections of eight mice. The macrophage layer surrounding extensive tumor necrosis showed the highest value, which was about 3.5 times that of the tumor cells. The second highest was the young granulation tissue with capillary vessels, fibroblasts and macrophages surrounding the tumor mass, which showed about a 2.4 times greater value than tumor cells followed by the necrotic area with macrophages, which showed about a 2.3 times greater value than tumor cells. The necrotic area with neutrophils, which were one of major phagocytes as well as macrophages, showed the lowest value. Semiquantitative morphometry of the microgram is included in Table 1. The macrophage layer were about 4.38 % and the granulation tissues were 3.55 % of the total area. It shows that about 24 % (4.38 %×3.5+3.55 %×2.4) of radioactivity for FDG in the whole section was derived from non-neoplastic cellular elements in tumor tissues.

Discussion

FDG accumulates not only in the tumor cells but also in the inflammatory cellular elements which appear in association with growth or necrosis of tumor. Accumulation of FDG is relatively higher in macrophages and young granulation tissue than in the tumor cells. These findings mean that the inflammatory cells in the tumor tissue more or less influence the tumor uptake of FDG. For precise analysis of FDG uptake in tumor-bearing subjects, especially after anti-neoplastic treatment, one should consider not only the tumor cells proper but also the non-neoplastic cellular elements.

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Table 1. FDG distribution in FM3A tumor tissue

	Grains/100 μm^2	Ratios	Area % of whole section	Radioactivity (%)	
Tumor cells	10.2±2.1	1.00	(70.39)	(76.24 - 78.41)	
Granulation tissue					
Fibroblasts	17.4±2.5*	1.79±0.57	3.55±3.00	6.35 - 8.52	21.59 - 23.76
Fibroblasts + macrophages	24.4±5.4*§	2.40±0.38			
Macrophages	36.2±8.8*	3.48±0.26	4.38±0.88	15.24	
Necrosis	-	-	21.68±8.51	-	
with Macrophages	23.1±2.7*	2.32±0.37	unmeasurable	-	
with Neutrophils	6.5±1.9**	0.65±0.20	unmeasurable	-	

n; 8 mice, Mean±S.D. of 8 to 12 various points in the tissue.

*: $p<0.001$, **: $p<0.005$ compared to Tumor cells.

§: $p<0.01$ compared to Macrophages.